RITUXAN®

Rituximab

WARNINGS

Fatal Infusion Reactions: Deaths within 24 hours of RITUXAN infusion have been reported. These fatal reactions followed an infusion reaction complex which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. (See WARNINGS and ADVERSE REACTIONS.)

Patients who develop severe infusion reactions should have RITUXAN infusion discontinued and receive medical treatment.

Tumor Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS following treatment with RITUXAN. (See WARNINGS.)

Severe Mucocutaneous Reactions: Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with RITUXAN treatment. (See WARNINGS and ADVERSE REACTIONS.)

DESCRIPTION

The RITUXAN® (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures. Rituximab drug product is manufactured from either bulk drug substance manufactured by Genentech, Inc. (US License No. 1048) or utilizing formulated bulk Rituximab supplied by IDEC Pharmaceuticals Corporation (US License No. 1235) under a shared manufacturing arrangement.

RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. RITUXAN is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

CLINICAL PHARMACOLOGY

General

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes.[1, 2] The antigen is also expressed on > 90% of B-cell non-Hodgkin's lymphomas (NHL),[3] but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues.[4] CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation,[4] and possibly functions as a calcium ion channel.[5] CD20 is not shed from the cell surface and does not internalize upon antibody binding.[6] Free CD20 antigen is not found in the circulation.[2]

Preclinical Pharmacology and Toxicology

Mechanism of Action: The Fab domain of Rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC)[7] and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.[8]

Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

Human Pharmacokinetics/Pharmacodynamics

In patients given single doses at 10, 50, 100, 250 or 500 mg/m^2 as an IV infusion, serum levels and the half-life of Rituximab were proportional to dose.[9] In 14 patients given 375 mg/m^2 as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range, 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to 407.0 hours); after the fourth infusion.[10,11,12] The wide range of half-lives may reflect the variable tumor burden among patients and the changes in CD20-positive (normal and malignant) B-cell populations upon repeated administrations.

RITUXAN at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 4 doses to 203 patients naive to RITUXAN. The mean C_{max} following the fourth infusion was 486 µg/mL (range, 77.5 to 996.6 µg/mL). The peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with nonresponders; however, no difference was found in the rate of elimination as measured by serum half-life. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

RITUXAN at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 8 doses to 37 patients. The mean C_{max} after 8 infusions was 550 µg/mL (range, 171 to 1177 µg/mL). The mean C_{max} increased with each successive infusion through the eighth infusion (Table 1).

Table 1

Rituximab C_{max} Values

Infusion Number	Mean C_{max} µg/mL	Range µg/mL
1	242.6	16.1-581.9
2	357.5	106.8-948.6
3	381.3	110.5-731.2
4	460.0	138.0-835.8
5	475.3	156.0-929.1
6	515.4	152.7-865.2
7	544.6	187.0-936.8
8	550.0	170.6-1177.0

The pharmacokinetic profile of RITUXAN when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with RITUXAN alone.

Administration of RITUXAN resulted in a rapid and sustained depletion of circulating and tissue-based B cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B cells in seven of eight patients who had received single doses of Rituximab $\geq$100 mg/m^2.[9] Among the 166 patients in the pivotal study, circulating B cells (measured as CD19–positive cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. Of the responding patients assessed (n = 80), 1% failed to show significant depletion of CD19–positive cells after the third infusion of Rituximab as compared to 19% of the nonresponding patients. B-cell recovery began at approximately 6 months

following completion of treatment. Median B-cell levels returned to normal by 12 months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following Rituximab administration. However, only 14% of patients had reductions in IgM and/or IgG serum levels, resulting in values below the normal range.

CLINICAL STUDIES

Studies with a collective enrollment of 296 patients having relapsed or refractory low-grade or follicular B-cell NHL are described below (Table 2). RITUXAN regimens tested include treatment weekly for 4 doses and treatment weekly for 8 doses. Clinical settings studied were initial treatment, initial treatment of bulky disease, and retreatment.

Table 2

Summary of RITUXAN Efficacy Data by Schedule and Clinical Setting (See ADVERSE REACTIONS for Risk Factors Associated with Increased Rates of Adverse Events.)

	Initial, Weekly x 4 N = 166	Initial, Weekly x 8 N = 37	Initial, Bulky, Weekly x 4 N = 39[1]	Retreatment, Weekly x 4 N = 60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration Of Response[2, 3, 4] (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

[1] Six of these patients are included in the first column. Thus, data from 296 intent to treat patients are provided in this table.

[2] Kaplan-Meier projected with observed range.

[3] "+" indicates an ongoing response.

[4] Duration of response: interval from the onset of response to disease progression.

Initial Treatment, Weekly for 4 doses

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory low-grade or follicular B-cell NHL who received 375 mg/m^2 of RITUXAN given as an IV infusion weekly for 4 doses.[13] Patients with tumor masses >10 cm or with >5,000 lymphocytes/μL in the peripheral blood were excluded from the study. The overall response rate (ORR) was 48% with 6% complete response (CR) and 42% partial response (PR) rates. The median time to onset of response was 50 days and the median duration of response was 11.2 months (range,

1.9 to 42.1+). Disease-related signs and symptoms (including B-symptoms) were present in 23% (39/166) of patients at study entry and resolved in 64% (25/39) of those patients.

In a multivariate analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF subtype A (58% vs. 12%), higher in patients whose largest lesion was <5 cm vs. >7 cm (maximum, 21 cm) in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared with chemoresistant (defined as duration of response <3 months) relapse (53% vs. 36%). ORR in patients previously treated with autologous bone marrow transplant was 78% (18/23). The following adverse prognostic factors were *not* associated with a lower response rate: age ≥60 years, extranodal disease, prior anthracycline therapy, and bone marrow involvement.

Initial Treatment, Weekly for 8 Doses

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m^2 of RITUXAN weekly for 8 doses. The ORR was 57% (CR 14%, PR 43%) with a projected median duration of response of 13.4 months (range, 2.5 to 36.5+).[14] (For information on the higher incidence of Grade 3 and 4 adverse events, see ADVERSE REACTIONS, Risk Factors Associated with Increased Rates of Adverse Events.)

Initial Treatment, Bulky Disease, Weekly for 4 Doses

In pooled data from multiple studies of RITUXAN, 39 patients with relapsed or refractory, bulky disease (single lesion >10 cm in diameter), low-grade NHL received 375 mg/m^2 of RITUXAN weekly for 4 doses. The ORR was 36% (CR 3%, PR 33%) with a median duration of response of 6.9 months (range 2.8 to 25.0+). (For information on the higher incidence of Grade 3 and 4 adverse events, see ADVERSE REACTIONS, Risk Factors Associated with Increased Rates of Adverse Events.)

Retreatment, Weekly for 4 Doses

In a multi-center, single-arm study, 60 patients received 375 mg/m^2 of RITUXAN weekly for 4 doses.[15] All patients had relapsed or refractory, low-grade or follicular B-cell NHL and had achieved an objective clinical response to a prior course of RITUXAN. Of these 60 patients, 55 received their second course of RITUXAN, 3 patients received their third course and 2 patients received their second and third courses of RITUXAN in this study. The ORR was 38% (10% CR and 28% PR) with a projected median duration of response of 15 months (range, 3.0 to 25.1+ months).

INDICATIONS AND USAGE

RITUXAN is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma.

CONTRAINDICATIONS

RITUXAN is contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of this product. (See WARNINGS.)

WARNINGS (See BOXED WARNINGS.)

Severe Infusion Reactions (See BOXED WARNINGS, ADVERSE REACTIONS and Hypersensitivity Reactions): RITUXAN has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reactions may include hypotension, angioedema, hypoxia or bronchospasm, and may require interruption of RITUXAN administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. In the reported cases, the following factors were more frequently associated with fatal outcomes:

female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle cell lymphoma.

Management of severe infusion reactions: The RITUXAN infusion should be interrupted for severe reactions and supportive care measures instituted as medically indicated (e.g., intravenous fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells ($\geq 25{,}000/mm^3$) with or without evidence of high tumor burden.

Tumor Lysis Syndrome [TLS] (See BOXED WARNINGS and ADVERSE REACTIONS): Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatasemia, have been reported within 12 to 24 hours after the first RITUXAN infusion. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with RITUXAN. The risks of TLS appear to be greater in patients with high numbers of circulating malignant cells ($\geq 25{,}000/mm^3$) or high tumor burden.

Prophylaxis for TLS should be considered for patients at high risk. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of the complications of TLS, RITUXAN has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Hypersensitivity Reactions:

RITUXAN has been associated with hypersensitivity reactions (non-IgE-mediated reactions) which may respond to adjustments in the infusion rate and in medical management. Hypotension, bronchospasm, and angioedema have occurred in association with RITUXAN infusion (see Severe Infusion Reactions). RITUXAN infusion should be interrupted for severe hypersensitivity reactions and can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non-life-threatening hypersensitivity reactions have been able to complete the full course of therapy. (See DOSAGE and ADMINISTRATION.) Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines

and corticosteroids, should be available for immediate use in the event of a reaction during administration.

Cardiovascular:

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of RITUXAN. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during RITUXAN therapy and should be monitored throughout the infusion and immediate post-infusion period.

Renal:

RITUXAN administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to a fatal outcome. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm^3) or high tumor burden who experience tumor lysis syndrome (see Tumor Lysis Syndrome) and in patients administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN is not an approved treatment regimen. If this combination is used in clinical trials *extreme caution* should be exercised; patients should be monitored

closely for signs of renal failure. Discontinuation of RITUXAN should be considered for those with rising serum creatinine or oliguria.

Severe Mucocutaneous Reactions (See BOXED WARNINGS and ADVERSE REACTIONS):

Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with RITUXAN. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy),[16] Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1 to 13 weeks following RITUXAN exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of readministration of RITUXAN to patients with any of these mucocutaneous reactions has not been determined.

PRECAUTIONS

Laboratory Monitoring: Because RITUXAN targets all CD20-positive B lymphocytes, malignant and nonmalignant, complete blood counts (CBC) and platelet counts should be obtained at regular intervals during RITUXAN therapy and more frequently in patients who develop

cytopenias (see ADVERSE REACTIONS). The duration of cytopenias caused by RITUXAN can extend well beyond the treatment period.

Drug/Laboratory Interactions: There have been no formal drug interaction studies performed with RITUXAN. However, renal toxicity was seen with this drug in combination with cisplatin in clinical trials. (See WARNINGS, Renal.)

HACA Formation: Human antichimeric antibody (HACA) was detected in 4 of 356 patients and 3 had an objective clinical response. The data reflect the percentage of patients whose test results were considered positive for antibodies to RITUXAN using an enzyme-linked immunosorbant assay (limit of detection = 7 ng/mL). The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RITUXAN with the incidence of antibodies to other products may be misleading.

Immunization: The safety of immunization with live viral vaccines following RITUXAN therapy has not been studied. The ability to generate

a primary or anamnestic humoral response to vaccination is currently being studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN, or to determine its effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following RITUXAN therapy.

Pregnancy Category C: Animal reproduction studies have not been conducted with RITUXAN. It is not known whether RITUXAN can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Human IgG is known to pass the placental barrier, and thus may potentially cause fetal B-cell depletion; therefore, RITUXAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether RITUXAN is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

Pediatric Use: The safety and effectiveness of RITUXAN in pediatric patients have not been established.

Geriatric Use: Among the 331 patients enrolled in clinical studies of single agent RITUXAN, 24% were 65 to 75 years old and 5% were 75 years old and older. The overall response rates were higher in older (age ≥ 65 years) vs. younger (age < 65 years) patients (52% vs. 44%, respectively). However, the median duration of response, based on Kaplan-Meier estimates, was shorter in older vs. younger patients: 10.1 months (range, 1.9 to 36.5+) vs. 11.4 months (range, 2.1 to 42.1+), respectively. This shorter duration of response was not statistically significant. Adverse reactions, including incidence, severity and type of adverse reaction were similar between older and younger patients.

ADVERSE REACTIONS

The most serious adverse reactions caused by RITUXAN include infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias and angina, and renal failure. Please refer to the BOXED WARNINGS and WARNINGS sections for detailed descriptions of these reactions. Infusion reactions and lymphopenia are the most commonly occurring adverse reactions.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Additional adverse reactions have been identified during postmarketing use of RITUXAN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to RITUXAN exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to RITUXAN.

Where specific percentages are noted, these data are based on 356 patients treated in nonrandomized, single-arm studies of RITUXAN administered as a single agent. Most patients received RITUXAN 375 mg/m^2 weekly for 4 doses. These include 39 patients with bulky disease (lesions $\geq$ 10 cm) and 60 patients who received more than 1 course of RITUXAN. Thirty-seven patients received 375 mg/m^2 for 8 doses and 25 patients received doses other than 375 mg/m^2 for 4 doses

414 and up to 500 mg/m^2 single dose in the Phase 1 setting. Adverse events
415 of greater severity are referred to as "Grade 3 and 4 events" defined by
416 the commonly used National Cancer Institute Common Toxicity Criteria.[17]